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LONG-TERM OUTCOMES OF ADJUVANT MITOTANE THERAPY IN PATIENTS WITH RADICALLY RESECTED ADRENOCORTICAL CARCINOMA.

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ABSTRACT

Context: in 2007, a large retrospective case-control study provided evidence that adjuvant mitotane prolongs recurrence-free survival (RFS) in patients with radically resected adrenocortical carcinoma (ACC).

Objective and design: We aimed to confirm the prognostic role of adjuvant mitotane in the same series after 9 additional years of follow-up.

Setting, Patients and Interventions: 162 ACC patients included in the previous study, who did not recur or die after a landmark period of 3 months, were considered. 47 patients were enrolled in 4 Italian centers where adjuvant mitotane was routinely recommended (mitotane group), 45 patients in 4 Italian centers where no adjuvant strategy was undertaken (control group 1), and 70 German patients left untreated after surgery (control group 2).

Main Outcome Measures: The primary aim was RFS, the secondary was overall survival (OS).

Results: at multivariate analysis, an increased risk of recurrence was found in both control cohorts (group 1: Hazard Ratio [HR] 2.98, 95% CI: 1.75-5.09, p <0.0001; group 2: HR 2.61, 95% CI: 1.56-4.36, p <0.0001) compared to the mitotane group. The risk of death was significantly higher in control group 1 (HR 2.03 95% CI:1.17-3.51 p = 0.011) but not in control group 2 (HR 1.60, 95% CI: 0.94-2.74, p = 0.083), which had better prognostic factors and more aggressive treatment of recurrences than control group 1. The benefit of adjuvant mitotane on RFS was observed regardless of the hormone secretory status.

Conclusions: adjuvant mitotane is associated with prolonged RFS, without any apparent influence by the tumor secretory status. The retrospective nature of the study is a major limitation.

INTRODUCTION

Radical surgery can potentially cure patients with ACC, a rare and aggressive endocrine malignancy (1). However, ACC has a high propensity to recur and tumor recurrence affects significantly life expectancy of ACC patients (2-4). Although complete tumor removal is an important prognostic factor, achieving a R0 status does not prevent disease recurrence (1-4). This provides a rationale for adjuvant therapy and mitotane, an adrenolytic drug with an established role in the treatment of patients with advanced ACC, has been used in the adjuvant setting (1).

In 2007, we reported the results of a multicenter, retrospective, case-control study comparing the outcome of ACC patients managed at some Italian centers, where adjuvant mitotane treatment was used following radical surgery, with that of patients managed at other Italian centers, where adjuvant strategies were not adopted. To further control for potential biases, a cohort of German patients who were treated with surgery only was added as a second control group (5). The main strength of this study was that it included patients whose treatment assignment was not related to their characteristics but to the center policy. Recurrence free survival (RFS) was significantly prolonged in the mitotane group when compared with both control groups. Therefore, the study provided evidence that adjuvant mitotane may be of benefit to patients with radically resected ACC. The retrospective nature of the study, however, does not allow to definitively support adjuvant mitotane treatment for all patients. The study renewed interest in adjuvant mitotane treatment, but attracted criticisms (1,6). A major concern was the duration of follow-up, which was considered not long enough due to a relatively low number of recurrences and deaths in patients receiving adjuvant mitotane.

In the present study, we report the long-term outcomes of the original patient series with 9 additional years of follow-up. The primary aim was to confirm the prognostic role of adjuvant mitotane therapy on RFS; secondary aims were to assess the effects of mitotane on overall survival (OS) and the predictive role of cortisol hypersecretion on mitotane efficacy.

PATIENTS AND METHODS

The study details were reported previously (5). Briefly, we reviewed the outcome of 102 consecutive patients with ACC who had undergone radical surgery at 8 tertiary referral centers in Italy from 1985 through 2003. Inclusion criteria were age greater than 18 years, pathological diagnosis of ACC and the availability of preoperative and postoperative computed tomographic (CT) or magnetic resonance imaging (MRI) scans. Exclusion criteria were macroscopically incomplete resection, incomplete tumor staging, concomitant cancers within the previous 5 years, clinically significant concomitant diseases, and adjuvant therapies other than mitotane. Forty-seven patients were enrolled in 4 centers where adjuvant mitotane was recommended irrespective of patient and tumor characteristics (mitotane group), while 55 patients were enrolled in 4 centers where no adjuvant strategy was undertaken after surgery (control group 1). The German control group comprised 75 ACC patients from the German Adrenocortical Carcinoma Registry with available information on diagnostic procedures, surgical outcomes, and follow-up similar to those used to evaluate the Italian study population (control group 2). The institutional ethics committee at each clinical center approved the study.

Complete resection was defined as no evidence of macroscopic residual disease on the basis of surgical reports, histopathological analysis, and postoperative imaging. All histologic diagnoses were confirmed by experienced pathologists and reviewed centrally in more than 75% of cases (6). Staging was reported according to the McFarlane–Sullivan criteria (4). Follow-up visits, including images, were performed every 6 months. Disease recurrence was defined as radiologic evidence of a new lesion during follow-up. Follow-up for this study was closed in December 2013.

The primary aim was to compare RFS, defined as the time elapsing from the date of surgery to the first documentation of recurrence, in patients who received adjuvant mitotane therapy with that of patients who did not. Secondary aims were OS, defined as the time elapsing from the date of surgery to the date of death. For both RFS and OS, patients who did not experience the event (recurrence or death, respectively) were censored at the time of last follow-up examination.

Data analysis was done using SPSS version 17 (SPSS Inc, IBM). RFS and OS were estimated according to the Kaplan-Meier method; the respective comparisons between groups were performed using the log-rank test. The Cox regression model was used to assess in univariate and multivariate analyses the predictive role of mitotane treatment, clinical and pathological variables on RFS and OS. The likelihood ratio was used to assess the significance of covariates included in each model. All p values are 2-sided and results were considered significant at $p \leq .05$. The Cox analysis was also used to assess the presence of heterogeneity in the prognostic effect of the cortisol excess in patients stratified according to hormone secretion. In these subgroups, any modification of the prognostic effect was assessed by including the appropriate covariate interaction terms in the model. To reduce the inherent bias of patients with early progression and

death, all survival analyses were performed with the landmark method, using a fixed landmark point at month 3. Patients who experienced the event (recurrence or death) before the landmark point were excluded from the analysis.

RESULTS

Of the 177 patients included in the original study (5), 15 recurred or died within the first 3 months (landmark point), 10 patients in the control group 1 and 5 patients in the control group 2, and were therefore excluded from the present analysis. Among the fully assessable 162 patients, 47 patients received adjuvant mitotane (mitotane group), 45 patients formed the control group 1, and 70 patients the control group 2. Patient characteristics are detailed in Table 1.

The mitotane group and control group 1 were well balanced with respect to tumor stage, hormone secretory status, and Weiss score. The control group 2 had a lower proportion of patients with stage III-IV ACC than the mitotane group. In addition, patients in the control group 2 were significantly older than patients in the mitotane group. There were no major differences in the surgical approach among the various groups as most patients of all groups underwent open surgery compared to laparoscopic surgery (mitotane group, 94%, control group 1, 96%, and control group 2, 89%, respectively).

The median follow-up period after surgery of surviving patients at the last follow-up examination was 141 months (range, 42 to 199) in the mitotane group, 142 months (range, 25 to 219) in the control group 1, and 128 months (range, 38 to 323) in the control group 2. Recurrence was documented in 121 patients (75%), 25 in the mitotane group (53%), 40 in the control group 1 (89%), and 56 in the control group 2 (80%), respectively. The pattern of recurrence between the 3 groups was comparable and is detailed in Table 2. Treatment of recurrence included more frequently surgery in both the mitotane group and control group 2 than control group 1 (64%, 66% and 35%, respectively).

Death from ACC was reported in 100 patients (62%): 23 in the mitotane group (49%), 36 (90%) in the control group 1 and 41 (59%) in the control group 2, respectively.

Mitotane was given following a low-dose regimen (7) and median duration of adjuvant treatment was 42 months (range 4-162 months). Of the mitotane-treated patients, 11 patients suspended treatment while being free of disease as a decision of the treating physicians (end of the planned course of therapy), 5 patients discontinued definitively mitotane for toxicity (1 for leucopenia, 1 for elevation in liver enzymes, 2 for general toxicity and 1 for neurological toxicity, respectively) and 2 discontinued mitotane at the time of disease recurrence. Mitotane was continued in the other patients with recurrent ACC. Adverse events of mitotane treatment are given in Table 3.

Mitotane treatment was associated with longer RFS compared with both control groups (Figure 1A). The median RFS was 42 months in the mitotane group, 17 months in the control group 1 (p <0.001), and 26 months in the control group 2 (p = 0.005). The median OS was 161 months in the mitotane group, compared with 65 months in the control group 1 (p = 0.007) and 92 months in the control group 2 (p = 0.28), respectively (Figure 1B).

Table 4 reports the results of the univariate and multivariate Cox analyses. Adjuvant mitotane treatment was an independent predictive factor for RFS in multivariate analysis after adjusting for age, sex and tumor stage. The risk of

recurrence was significantly higher either in the control group 1 (Hazard Ratio [HR] 2.98, 95% Confidence Interval [CI]: 1.75-5.09, p <0.0001) or in the control group 2 (HR 2.61, 95% CI: 1.56-4.36, p <0.0001) when compared with the mitotane group.

Adjuvant mitotane treatment was also an independent predictive factor for OS in multivariate analysis after adjusting for age, sex and tumor stage. In comparison to the mitotane group, the risk of death was significantly higher in the control group 1 (HR 2.03, 95% CI:1.17-3.51 p = 0.011) but not in the control group 2 (HR 1.60, 95% CI: 0.94-2.74, p = 0.083).

The efficacy of adjuvant mitotane was also explored stratifying patients according to cortisol secretion by ACC in 137 evaluable patients. Mitotane effect on RFS did not differ according to the presence of overt cortisol excess. The risk of recurrence was higher in control groups 1 and 2 than in the mitotane group, both in patients with non-secreting tumors (HR 2.16, 95% CI: 1.12-4.17, p = 0.022 and HR 2.00, 95% CI: 0.93-4.34, p = 0.077, respectively) and in patients with cortisol-secreting ACC (HR 4.51, 95% CI: 1.92-10.60, p = 0.001 and HR 1.79, 95% CI: 0.86-3.73, p = 0.12, respectively). When assessing HR values in control group 2, it has to be considered that only 45 out of 70 patients (64%) were evaluable for ACC secretion.

DISCUSSION

The evidence on adjuvant mitotane therapy after radical resection of ACC is sparse and flawed by several limitations, such as limited statistical power, absence of a matched control group, RFS not uniformly defined and response duration unclearly reported. Moreover, all studies but one were retrospective and employed different formulations of mitotane at variable doses, ranging from 3 to 20 grams daily (Table 5). On this scenario, the most informative data were provided by our retrospective case-control study involving a large cohort of ACC patients who were assigned to adjuvant mitotane or no treatment independently on patient's characteristics (5). The study included a group of mitotane-treated patients and 2 contemporary, control groups of untreated patients matched for the major prognostic factors (actually the control group 2 had better prognostic features). This is strength of the study, since in other studies the presence of unfavorable characteristics was likely a factor supporting the decision to prescribe adjuvant mitotane and this have introduced biased data (Table 3). Very recently, Postlewait et al. (23) reported a retrospective analysis of the outcomes of 207 ACC patients who underwent resection at 13 centers in the US. They found that adjuvant mitotane was associated with decreased RFS and OS. The difference with our results may be readily explained by the selection of patients at unfavorable prognosis for mitotane treatment. The patients who were treated with mitotane had a higher frequency of stage IV, metastatic tumors and indeed chemotherapy was frequently associated to mitotane therapy. Also the frequency of cortisol excess, another negative prognostic factor, was more frequent in the mitotane group. Since 42% of the 88 patients treated with mitotane had stage IV ACC, this series is not comparable to our ones, with only 13% stage IV ACC.

Though the retrospective nature of our study is a major limitation, the rarity of ACC makes challenging the organization of a prospective randomized clinical trial. As a matter of fact, we are currently undertaking the first randomized, controlled trial in patients with ACC following radical extirpation, the ADIUVO study (www-adiuvo-trial.org), but recruitment is difficult and results are not expected before several years. Meanwhile, physicians who are treating ACC are left with the dilemma of prescribing or not post-operative mitotane treatment (6). To provide guidance in this controversial area, a panel of experts recommended adjuvant mitotane in radically resected ACC patients at high risk of recurrence (24), and this recommendation has been incorporated in currently available guidelines (1, 25).

Therefore, we re-analyzed the outcome data of the original patient cohorts after a longer follow-up, more than 9 years after the end of the original study.

To reduce the "immortal-time" bias, in the updated analysis we calculated RFS and OS estimates from the time point of 3 months (landmark method), thus excluding from the analysis the patients with early progression and death. We set the landmark point at 3 months because at that time mitotane treatment has been started in all patients. With the introduction of the landmark analysis the median RFS of patients in the control group 1 increased consistently in this

study as opposed to the original one (17 vs 10 months) while the difference was marginal in the control group 2 (26 vs 25 months). Even with the introduction of a landmark analysis and after a median follow-up of more than 10 years, the significant advantage in terms of reduction of the risk of recurrence of patients who underwent adjuvant mitotane compared to patients of both control groups was confirmed both in univariate and multivariate analyses. Mitotane treated patients had also a significant longer survival than patients included in the control group 1, while the survival advantage over the control group 2 just failed to attain the statistical significance. However, the control group 2 had a better risk profile, with a significantly higher percentage of stage I-II tumors, portending improved outcome. Moreover, treatment of recurrences was more aggressive in the control group 2 than in control group 1. Although the pattern of recurrence between the 3 groups was comparable, with local recurrences found in about 50% of cases, surgery was most frequently used in both the mitotane group and control group 2 than in control group 1 (64%, 66% and 35%, respectively). Since surgical approaches are generally regarded as superior to treatment regimens consisting only of medical therapy to manage recurrent ACC (**2, 26, 27**), we may argue that this difference in the management contributed to the better overall survival observed in the control group 2 than control group 1.

The recently published experience of the University of Michigan with adjuvant therapies for ACC shows that adjuvant mitotane treatment was associated with a significantly prolonged RFS in multivariate analysis (HR 0.723, 95%CI: 0.533-0.981, $p = 0.037$) although the effect on OS did not reach levels of significance (HR 0.887, 95% CI: 0.621-1.268, $p = 0.511$) (22).

Another point of controversy is whether mitotane could be better suited to treat secreting ACC, due to its inhibitory effects on adrenal steroidogenesis. In a French series of 166 patients, mitotane was not effective in improving RFS in the overall cohort, although in the subgroup of patients with cortisol excess a tendency towards a beneficial effect was seen (18). This finding raised the issue that the efficacy of adjuvant mitotane therapy may be limited to patients with cortisol-secreting tumors. However, cortisol was not a predictor of adjuvant mitotane efficacy in a large, multicenter, dataset recently published (**28**). In the present study, the efficacy of mitotane on RFS did not differ when patients were stratified by presence of cortisol excess. These data further support the antineoplastic activity of mitotane irrespective of the cortisol secretory status.

In conclusion, this updated analysis with longer follow-up and landmark analysis confirms that among patients with macroscopically complete removal of ACC, the use of adjuvant mitotane compared with observation is associated with prolonged RFS independently of hormone activity. We think that the present results strengthen the recommendation of adjuvant mitotane as part of the post-operative management of ACC patients. **Another important finding is that an aggressive use of surgery to treat ACC recurrences may be associated with prolonged survival. Repeat surgery for recurrent ACC may provide a benefit in overall survival independently from mitotane use.** These data are of

particular interest for surgeons operating on ACC patients, who should refer these patients to centers with specific expertise **on surgical treatment of ACC and management of mitotane therapy**. Interestingly, early referral of stage II ACC patients to specialized centers has been associated with an improved outcome (20). The retrospective nature of the study does not allow to establish definitively the value of adjuvant mitotane treatment. There might be subsets of patients, i.e. patients with small, low-grade tumors, who may not benefit from a strategy of adjuvant mitotane treatment. A currently ongoing randomized trial (ADIUVO study) is specifically aiming to establish mitotane efficacy in patients at low/intermediate risk of recurrence.

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REFERENCES

1. Berruti A, Baudin E, Gelderblom H, Haak HR, Porpiglia F, Fassnacht M and Pentheroudakis G. on behalf of the ESMO Guidelines working group. Adrenal cancer: ESMO Clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; Suppl 7:131-138.

2. Schulick RD, Brennan MF. Long-term survival after complete resection and repeat resection in patients with adrenocortical carcinoma. Ann Surg Oncol 1999; 6: 719-726.

3. Icard P, Goudet P, Charpenay C, Andreassian B, Carnaille B, Chapuis Y, Cougard P, Henry JF, Proye C. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. World J Surg 2001; 25:891-897.

4. Fassnacht M, Johanssen S, Quinkler M, Bucsky P, Willenberg HS, Beuschlein F, Terzolo M, Mueller HH, Hahner S, Allolio B for the German Adrenocortical Carcinoma Registry Group and the European Network for the Study of Adrenal Tumors. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification. Cancer 2009; 115:243-250.

5. Terzolo M, Angeli A, Fassnacht M, Daffara F, Tauchmanova L, Conton PA, Rossetto R, Buci L, Sperone P, Grossrubatscher E, Reimondo G, Bollito E, Papotti M, Saeger W, Hahner S, Koschker AC, Arvat E, Ambrosi B, Loli P, Lombardi G, Mannelli M, Bruzzi P, Mantero F, Allolio B, Dogliotti L, Berruti A. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med 2007; 356:2372-2380.

6. Huang H, Fojo T. Commentary: adjuvant mitotane for adrenocortical cancer a recurring controversy. J Clin Endocrinol Metab 2008; 93:3730-3732.

7. Terzolo M, Pia A, Berruti A, Osella G, Alì A, Carbone V, Testa E, Dogliotti L, Angeli A. Low-dose monitored mitotane treatment achieves the therapeutic range with manageable side effects in patients with adrenocortical cancer. J Clin Endocrinol Metab 2000; 85:2234-2238.

8. Schteingart DE, Motazedi A, Noonan RA, Thompson NW. Treatment of adrenal carcinomas. Arch Surg 1982; 117:1142-1146.

9. Venkatesh S, Hickey RC, Vassilopoulou-Sellin R, Fernandez JF, Samaan NA. Adrenal cortical carcinoma. Cancer 1989; 64:765-769.

316 10. Bodie B, Novick AC, Pontes JE, Straffon RA, Montie JE, Babiak T, Sheeler L, Schumacher P. The Cleveland
317 Clinic experience with adrenal cortical carcinoma. J Urol 1989; 141:257-260.

318 11. Pommier RF, Brennan MF. An 11-year experience with adrenocortical carcinoma. Surgery 1992; 112:963–970.

319 12. Vassilopoulou-Sellin R, Guinee VF, Klein MJ, Taylor SH, Hess KR, Schultz PN, Samaan NA. Impact of adjuvant
320 mitotane on the clinical course of patients with adrenocortical cancer. Cancer 1993; 71:3119-3123.

321 13. Haak HR, Hermans J, van de Velde CJ, Lentjes EG, Goslings BM, Fleuren GJ, Krans HM. Optimal treatment of
322 adrenocortical carcinoma with mitotane: results in a consecutive series of 96 patients. Br J Cancer 1994; 69:947-
323 951.

324 14. Barzon L, Fallo F, Sonino N, Daniele O, Boscaro M. Adrenocortical carcinoma: experience in 45 patients.
325 Oncology 1997; 54:490-496.

326 15. Dickstein G, Shechner C, Arad E, Best LA, Nativ O. Is there a role for low doses of mitotane (o,p0-DDD) as
327 adjuvant therapy in adrenocortical carcinoma? J Clin Endocrinol Metab 1998; 83:3100-3103.

328 16. Kasperlik-Zaluska AA. Clinical results of the use of mitotane for adrenocortical carcinoma. Braz J Med Biol Res
329 2000; 33:1191-1196.

330 17. Baudin E, Pellegriti G, Bonnay M, Penfornis A, Laplanche A, Vassal G, Schlumberger M. Impact of monitoring
331 plasma 1, 1-dichlorodiphenil-dichloroethane (o,p0-DDD) levels on the treatment of patients with adrenocortical
332 carcinoma. Cancer 2001; 92:1385-1392.

333 18. Bertherat J, Coste J, Bertagna X. Adjuvant mitotane in adrenocortical carcinoma. N Engl J Med 2007; 357:1256-
334 1257.

335 19. Grubbs EG, Callender GG, Yan Xing Y, Perrier ND, Evans DB, Phan AT, Lee JE. Recurrence of adrenal cortical
336 carcinoma following resection: surgery alone can achieve results equal to surgery plus mitotane. Ann Surg Oncol
337 2010; 17:263-270.

338 20. Fassnacht M, Johanssen S, Fenske W, Weismann D, Agha A, Beuschlein F, Führer D, Jurowich C, Quinkler M,
339 Petersenn S, Spahn M, Hahner S, Allolio B, German ACC Registry Group. Improved survival in patients with stage
340 II adrenocortical carcinoma followed up-prospectively by specialized centers. J Clin Endocrinol Metab 2010;
341 95:4925-4932.

21. Wangberg B, Khorram-Manesh A, Jansson S, Nilsson B, Nilsson O, Jakobsson CE, Lindstedt S, Odén A, Ahlman H. The longterm survival in adrenocortical carcinoma with active surgical management and use of monitored mitotane. Endocr Relat Cancer 2010; 17:265-272.

22. Else T, Williams AR, Sabolch A, Jolly S, Miller BS, Hammer GD. Adjuvant therapies, patient and tumor characteristics associated with survival of adult patients with adrenocortical carcinoma. J Clin Endocrinol Metab 2014; 99:455-461.

23. Postlewait LM, Ethun CG, Tran TB, Prescott JD, Pawlik TM, Wang TS, Glenn J, Hatzaras I, Shenoy R, Phay JE, Keplinger K, Fields RC, Jin LX, Weber SM, Salem A, Sicklick JK, Gad S, Yopp AC, Mansour JC, Duh QY, Seiser N, Solorzano CC, Kiernan CM, Votanopoulos KI, Levine EA, Staley CA, Poultsides GA, Maithel SK. Outcomes of Adjuvant Mitotane after Resection of Adrenocortical Carcinoma: A 13-Institution Study by the US Adrenocortical Carcinoma Group. J Am Coll Surg. 2016; 222(4): 480-90.

24. Berruti A, Fassnacht M, Baudin E, Hammer G, Haak H, Leboulleux S, Skogseid B, Allolio B, Terzolo M. Adjuvant therapy in patients with adrenocortical carcinoma: a position of an international panel. J Clin Oncol. 2010; 28 (23):e401-2

25. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Neuroendocrine Tumors Version 1.2015, 11/11/14 © National Comprehensive Cancer Network, Inc. 2014, NCCN.org.

26. Bellantone R, Ferrante A, Boscherini M, Lombardi CP, Crucitti P, Crucitti F, Favia G, Borrelli D, Boffi L, Capussotti L, Carbone G, Casaccia M, Cavallaro A, Del Gaudio A, Dettori G, Di Giovanni V, Mazziotti A, Marrano D, Masenti E, Miccoli P, Mosca F, Mussa A, Petronio R, Piat G, Marazano L, et al. Role of reoperation in recurrence of adrenal cortical carcinoma: results from 188 cases collected in the Italian National Registry for Adrenal Cortical Carcinoma. Surgery. 1997; 122(6): 1212-8.

27. Erdogan I, Deutschbein T, Jurowich C, Kroiss M, Ronchi C, Quinkler M, Waldmann J, Willenberg HS, Beuschlein F, Fottner C, Klose S, Heidemeier A, Brix D, Fenske W, Hahner S, Reibetanz J, Allolio B, Fassnacht M; German Adrenocortical Carcinoma Study Group. The role of surgery in the management of recurrent adrenocortical carcinoma. J Clin Endocrinol Metab. 2013; 98(1): 181-91.

28. Berruti A, Fassnacht M, Haak H, Else T, Baudin E, Sperone P, Kroiss M, Kerkhofs T, Williams AR, Ardito A, Leboulleux S, Volante M, Deutschbein T, Feelders R, Ronchi C, Grisanti S, Gelderblom H, Porpiglia F, Papotti M,

Hammer GD, Allolio B, Terzolo M. Prognostic role of overt hypercortisolism in completely operated patients with adrenocortical cancer. Eur Urol 2014; 65:832-838.

REFERENCES

- Figure 1A: Recurrence-free survival of adjuvant mitotane group and control groups

- Figure 1B: Overall survival of adjuvant mitotane group and control groups